Unexpected Silent Infarctions after Embolization of Cerebral Arteriovenous Malformations and Fistulas

A Diffusion-Weighted Magnetic Resonance Imaging Study

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Summary

We investigated the number and possible causes of clinically silent lesions seen in diffusion-weighted magnetic resonance imaging after embolization of arteriovenous malformations (AVMs) and fistulas using acrylate only or in combination with coils.

Included were 19 patients with 18 AVMs and one case of a vein of Galen aneurysm in which 25 interventions were carried out. Results of diffusion-weighted imaging, the appearance of perinidal and distant lesions, were correlated to Spetzler grade, nidus size, flow, number of feeders occluded, rate of nidus occlusion and duration of the intervention.

We found seven distant lesions corresponding to non-symptomatic infarcts in the given clinical setting. The only significant correlation between lesion size and parameters analyzed was the degree of nidus occlusion achieved during the intervention.

Because most of the lesions presented in cases with a high occlusion rate, they appear to be related to the intention to reach a complete occlusion of the nidus. These results emphasize that the risk involved in eliminating the nidus completely must be reconsidered with special care, particularly in a situation where most high-flow feeders have been occluded.

Introduction

Although endovascular interventions in cerebral arteriovenous malformations (AVMs) and fistulas (AVFs) have been carried out for over 20 years, their indication as palliative or definite therapy or adjuvant measure before neurosurgery or stereotactic radiation remains a matter of debate [1,2]. Fortunately, complications like clinically symptomatic haemorrhage or stroke are not frequently seen after endovascular interventions in these lesions [3]. The overall frequency of post-interventional ischaemic brain lesions however has been reported to reach 22% [4]. This unexpectedly high number was mainly due to clinically non-apparent ischaemia detected by diffusion-weighted magnetic resonance imaging (DW-MRI). The sensitivity of this method in depicting early cerebral ischaemia has been demonstrated not only after interventions, but also in otherwise uneventful diagnostic cerebral angiographies showing new lesions in 26% which were only visible in DW-MRI [5]. In experienced hands and using new material and modern equipment, this figure can be reduced to 2% [6].

The aim of the present investigation was to assess the risk of unexpected and clinically silent brain infarctions after embolization of brain AVMs and AVFs only shown in DW-

MRI. If a similar high number of silent ischaemias could be detected as reported after interventions in cerebral aneurysms ranging from 20% up to 100% [7-9], we have to look more for possible risk factors like grade and size of the lesion, vascular supply and degree of flow reduction achieved.

Patients and Methods

This prospective study started in the beginning of 2010 after approval by the national ethical committee, and was conducted over two and a half years. During this time, we performed 70 interventions in 54 patients with AVMs or AVFs.

Patients and Interventions

Having excluded all cases without appropriate MR imaging and those with new neurologic deficit on the day following the intervention, all patients where only extracranial arteries were occluded and those treated without glue injections, 18 patients with AVMs and one patient with a vein of Galen aneurysm (VOGA) containing multiple fistulous shunts remained for analysis. Ten of these patients were treated after haemorrhages (two acute interventions during the first three days after bleeding, the other with a delay of at least one month) and seven because of convulsions, combined with cognitive deterioration in two of them. The VOGA patient was embolized because of increasing cardiac problems. Only one AVM was an incidental finding. All interventions were carried out using n-butyl-2-cyanoacrylate or as combined glue and transarterial coil embolizations. Thirteen of the 18 AVMs and the VOGA were high-flow lesions, whereas the other five AVMs were low-flow lesions. Two patients were embolized twice and two others three times during the study, so that at the end, the report is based on 25 interventions. Because some patients had been embolized before inclusion in the study, no previous intervention had been carried out only in half of the procedures included. Further details on patients' age and gender and Spetzler classification of the AVMs are listed in Table 1.

The embolizations were intended to achieve definitive occlusion of the AVMs/AVFs in nine interventions, whereas in the majority of cases, they served as adjuvant measures before later neurosurgery or gamma knife radiosurgery. In all cases, the guiding catheters (Envoy® or Fasguider®) could be introduced into the internal carotid or vertebral arteries without difficulty. For superselective catheterization, we used Spinnaker® (1.5 and 1.8 French) catheters and Mirage® (0.8 French) guide wires. Embolizations were performed by a mixture of Histoacryl® and Lipiodol®. Patients were not anticoagulated systematically, but the catheters were continuously flushed by saline containing 1000 units of heparin per litre. The number of feeding arteries occluded ranged from one to five. The intervention duration was taken as the interval between the first and last series of angiograms. Shunt reduction was quantified on a ten-point scale by two experienced interventionalists (LS and PS in consensus) blinded to the MR results by comparison of the first and last angiographic series taking into account the nidus size as well as the flow velocity of the contrast agent. Finally, both raters consistently classified shunt reduction as low (0-30%), medium (40-70%) or high (80-100%). According to these findings, we achieved a high shunt reduction in nine AVMs, a medium reduction in seven AVMs and a low reduction in the other eight AVMs and the VOGA. All interventions were tolerated well without apparent clinical complications showing up at the neurologic examination on the following day.

MR Imaging

Having received informed consent from the patients scheduled for an embolization, MR imaging was performed on a 3 Tesla system

Table 1 **Patients included in the study and characterization of AVMs/VOGA.**

No. of patients* (f : m)	Age (mean, range)	Shunt (high : low flow)	No. of feeding arteries	Spetzler Grade of 18 AVMs				
				I	II	III	IV	V
19 (8 : 11)	30.5 (7-58)	14 : 5	3.6 (1-10)	4	7	4	1	2

** Two of these patients were embolized twice and two patients three times (=25 interventions).*

(Achieva, Philips Medical Systems) within 24 hours after the intervention. Apart from the routine imaging which consisted of T2-, FLAIR- and T1-weighted (3D Turbo Field Echo) scans and time-of-flight angiography, diffusion-weighted scans were measured using a single shot echo planar imaging-based spin echo sequence (TR/TE 2508/65 ms, slice thickness 4 mm, field of view 230, measured voxel size 1.8×1.8 mm, b-values 0 and 1000 s/mm^2).

Evaluation

From the data measured by the diffusion-weighted sequence, maps of the apparent diffusion coefficient (ADC) were calculated by scanner-inherent software.

The DWI scans and ADC maps were checked for areas of reduced diffusion within and outside the nidus, and according to their localization separated into intra- or perinidal lesions and distant lesions.

In case of positive distant findings, two neuroradiologists blinded to the angiographic results measured the extension of the lesions using ImageJ (http://rsb.info.nih.-gov/ij). For correlation between size of the lesions and age, nidus properties and achieved rate of occlusion, we calculated the Spearman's rank correlation coefficient setting the threshold of significance at 95%.

Because of the small number of combined glue and coil embolizations (two interventions), the contribution of coils was not evaluated as an independent variable.

Results

Except for four interventions, small bright intra- or perinidal areas could be detected on the post-procedural DW-MRI scans, which were mainly localized within or at the edge of the nidus, often corresponding to occluded veins (Table 2).

Distant areas of reduced diffusion (hyperintense in DW-MRI with clearly reduced values in the ADC maps) were seen after seven interventions in seven different patients. In case of multiple interventions, they always showed up after the last one. In five of these patients, the AVMs had been diagnosed because of previous haemorrhage (all of them after an interval of more than one month) and in two of them because of convulsions. All lesions but one were localized in an area supplied by distal branches originating from the targeted feeder. In one case, however, a partial occlusion of the pericallosal artery giving rise to multiple feeders had been achieved unintentionally.

Two of these areas were tiny (around 0.5 cm^3 in size) and affected the parietal and frontal cortex, respectively. In both cases, afferent branches of the middle cerebral artery had been embolized (two and three branches) with a shunt reduction rate of 80% and 10%, both in medium-sized AVMs.

In five cases however, the DW-MRI hyperintensities were larger, between 1.3 and 21 cm^3, and affected the cortex as well as the adjacent white matter. Three of these AVMs were small (3.5 to 6.6 cm^3), and after embolization of one

Table 2 **Correlation between frequency of DW-MRI positive findings and Spetzler grade, size of nidus/fistula, number of feeding arteries occluded and reduction of shunt as estimated by angiography in 25 interventions.**

25 interventions in AVMs (Spetzler grade) and AVFs	Size of nidus/ fistula in 25 interventions	Flow of AVMs/ AVFs in 25 interventions	No. of arteries occluded in 25 interventions	Shunt reduction in 25 interventions	Duration of intervention (in min)
AVM, I-II: 12 (4)	< 10 cm^3: 11 (3)	High: 19 (5)	1: 11 (2)	10-30%: 9 (2)	< 60: 12 (3)
III: 5 (2)	10-30 cm^3: 3 (2)	Low: 6 (2)	2: 6 (3)	40-70%: 7 (0)	60 – 90: 8 (1)
IV-V: 7 (1)	> 30 cm^3: 10 (2)		>2: 8 (2)	80-100%: 9 (5)	90-120: 4 (3)
VOGA: 1 (0)	< 10 cm^3 (0)				>120: 1 (0)
ρ = 0.178	ρ = 0.197	ρ = 0.314	ρ = 0.324	ρ = 0.476, p < 0.05	ρ = 0.297

Number of cases with extranidal lesions is given in brackets. ρ = Spearman's rank correlation coefficient between size of extranidal lesion and parameter indicated.

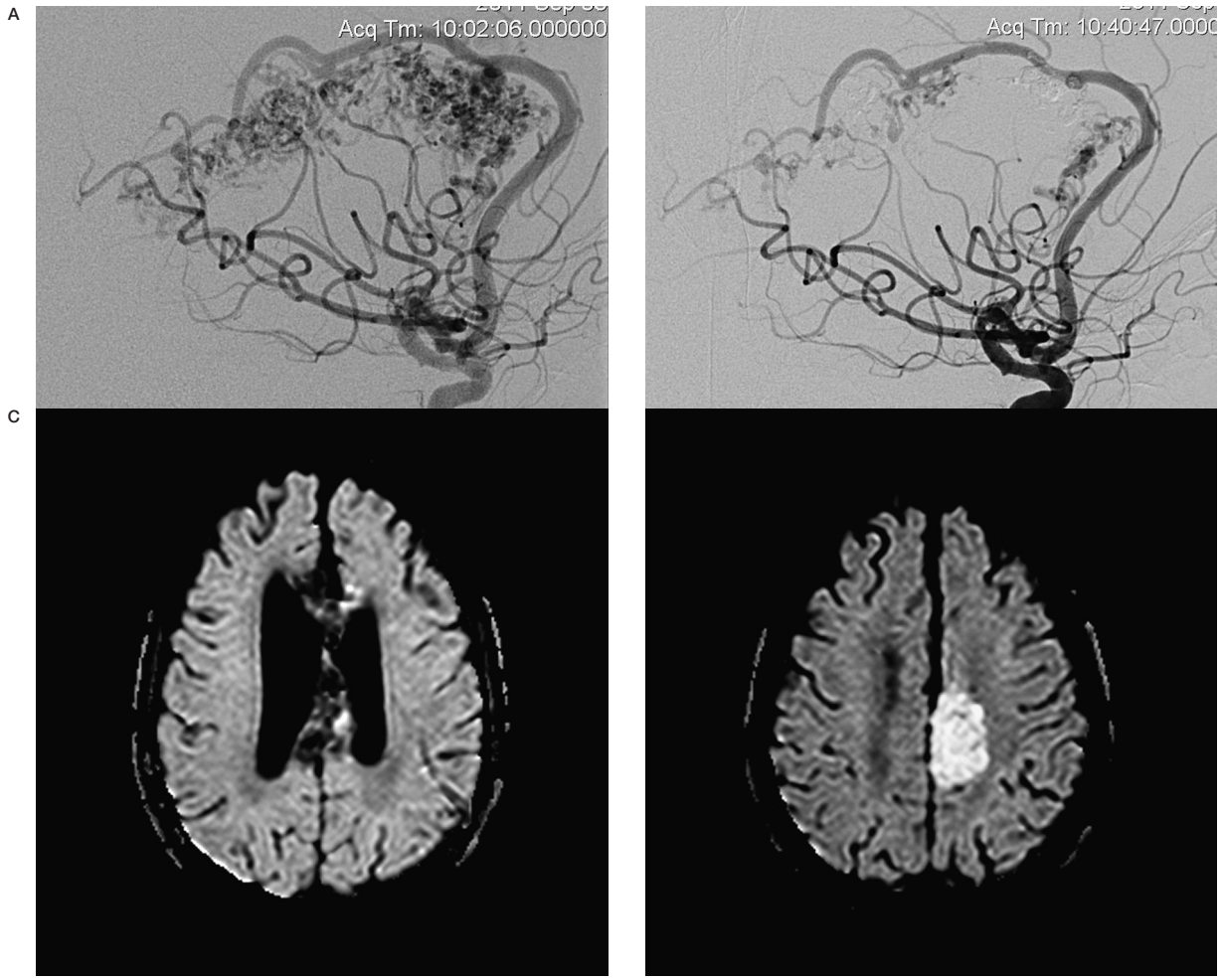

Figure 1 Intra- and extranidal lesions in DW-MRI after a second embolization of a pericallosal AVM in a 28-year-old male. According to pre- and post-interventional angiograms (A, B), the nidus occlusion rate was estimated to 80%. DW-MRI (C , D) showed small intra- and perinidal hyperintensities probably corresponding to occluded vessels and a larger extranidal lesion representing an infarction.

to four branches, the shunt had been reduced by 90 % in all cases. The two other AVMs were larger (45 and 72 cm^3), and after an embolization of two supplying arteries, both showed a shunt occlusion of 80% and 30%, respectively (Figure 1).

Correlation analysis for extension of the distant areas of reduced diffusion to age, size of the nidus, Spetzler grade, pre-interventional flow and number of afferent arteries gave weak results ($\rho \leq 0.324$), but there was a significant positive correlation to the degree of nidus occlusion ($\rho = 0.463$, $p<0.05$).

Discussion

In a recent meta-analysis of embolizations carried out in AVMs, complications leading to permanent neurological deficit or death occurred in a median 6.6 % (0 % to 28%) of patients [10]. This rate is in between the figures of complications after microsurgery (7.4%) and stereotactic radiation (5.1 %). However, from 29 new deficits observed after a presurgical intervention in 14% of patients, which were mainly caused by peri or post-procedural haemorrhage, only one third was significant,

and most of them resolved over time [11]. Clinically apparent complications were found to be more frequent in case of deep venous drainage, high Spetzler grade and periprocedural bleedings [12,13] and also to depend on the number of feeders embolized [14].

The high sensitivity of DW-MRI to demonstrate acute cerebral infarctions is well-known [15,16]. After embolizations of AVMs and AVFs, all distant extranidal areas of increased intensity in DW-MRI with corresponding reduced diffusion values in the calculated ADC-maps, may be regarded as acute ischaemic lesions, if haemorrhages or thrombosed veins are excluded [4].

For clarification, we point out once more that clinically apparent complications were not in the focus of the present study. By contrast, we were interested to see how often "footprints" of disturbed perfusion [17] could be found after technically uneventful procedures without clinical deficit which otherwise are regarded as completely uneventful. As we did not perform follow-ups during the present study, we can only speculate on the nature of the distant lesions. The five larger extranidal DW-MRI abnormalities represent true - although clinically silent - infarctions and the two small cortical areas of reduced diffusion may correspond to those remnants described after a TIA [17] without permanent clinical consequences. But even in case of reversibility, such "footprints" are indications of some sort of vascular compromise, and it appears justified to look further into their possible cause of origin.

The frequency of such DW-MRI lesions with a distant extranidal localization seen in our study (seven in 19 patients or in 28% of all 25 interventions) is slightly higher than that reported by Cronquist et al. [4] (9/21 patients or 22% of all procedures). Their study also included symptomatic infarctions. One reason for this higher number of "silent" infarctions may be the relatively low frequency of such interventions in our institution (around 20 per year).

A second reason for the rather high frequency of distant lesions could be the fact that we tried to achieve a complete occlusion in more than one third of cases. All distant lesions were located in areas supplied by branches arising from the targeted feeders. Retrospective analysis of the angiograms showed glue overflow in one case where we tried to reach the nidus through newly-formed collaterals, and a relatively proximal position of the catheter tip in a second one with an unintended partial occlusion of more proximal parts of the main feeder.

The remaining five of the seven distant areas of reduced diffusion, which we cannot attribute to technical problems during angiography, were seen in those nine interventions in which an occlusion of 80% or more was achieved. This close relation is underlined by the correlation analysis showing significance only between the size of the distant lesion and the occlusion rate achieved. Apart from some "over-embolization" which can never be excluded, progressive arterial or venous thrombosis might have been involved as well as arterial spasm.

Some of the lesions may have been prevented by post-procedural anticoagulation, as proposed post-surgically for AVMs with extensive venous drainage networks [18]. If a completely safe position of the catheter tip cannot be reached at some stage, the risk of a possible or even deliberate occlusion of some extranidal arteries supplying non-eloquent territories could be justified, but only in very special circumstances. This may be the case if for some economic or logistic reasons the endovascular approach is the only treatment that can be offered. However, in most conditions one could reconsider the intention of a complete occlusion and leave the rest of the AVM for neurosurgery or stereotactic radiation [19-21].

Conclusion

Our study showed a high number (nearly 30%) of areas of increased signal at some distance from the nidus in DW-MRI after the embolization of AVMs and one VOGA, corresponding to clinically silent infarctions. Because most of these lesions appeared to be related to the intention to reach a complete occlusion of the nidus, the glue injections at the end of the intervention seem to be the most dangerous. In this situation where most high-flow feeders are already occluded, special care must be taken to reconsider the risk involved in eliminating the nidus completely and hopefully cure the patient.

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